PSJ17 Exh 49

Cephalon

September 24, 2003

Division of Anesthetic, Critical Care and
Addiction Drug Products, HFD-170
Attention: Document Control Room 9B23
Food and Drug Administration
5600 Fishers Lane
Rockville, MD 20857

Re: NDA 20-747
Actiq® (oral transmucosal fentanyl citrate, OTFC®)
Risk Management Program – Quarterly Report

Dear Sir/Madam:

Reference is made to Section 10 of the Risk Management Program (RMP) dated February 9, 1999 (Supplement No. S-003 dated February 10, 1999), in which we commit to provide a quarterly report of this document. Therefore, the purpose of this communication is to submit the 17th quarterly report for the Actiq Risk Management Program. This report covers the period from April 1, 2003 through June 30, 2003.

If you have any questions regarding this submission, please contact me at 610-738-6237 or Ms. Tracie Parker at 610-738-6339.

Sincerely,

Carol S. Marchione

Carol S. Marchione
Senior Director
Regulatory Affairs

Encl.

Exhibit 009
TEVA
WITNESS: MARCHIONE
DATE: 1/18/19
REPORTER: Amanda Miller CRr

Cephalon, Inc. • 145 Brandywine Parkway • West Chester, PA 19380-4245 • (610) 344-0200 • Fax (610) 344-0065

DEPARTMENT OF HEALTH AND HUMAN SERVICES
FOOD AND DRUG ADMINISTRATION

APPLICATION TO MARKET A NEW DRUG, BIOLOGIC, OR AN ANTIBIOTIC DRUG FOR HUMAN USE

(Title 21, Code of Federal Regulations, 314 & 601)

Form Approved: OMB No. 0910-0338
Expiration Date: March 31, 2003
See OMB Statement on page 2

FOR FDA USE ONLY
APPLICATION NUMBER
20-747

APPLICANT INFORMATION

NAME OF APPLICANT	DATE OF SUBMISSION
Cephalon, Inc	September 24, 2003
TELEPHONE NO *(Include Area Code)*	**FACSIMILE (FAX) Number** *(Include Area Code)*
610-344-0200	610-738-6642
APPLICANT ADDRESS *(Number, Street, City, State, Country, ZIP Code or Mail Code, and U.S. License number if previously issued)*	**AUTHORIZED U.S. AGENT NAME & ADDRESS** *(Number, Street, City, State, ZIP Code, telephone & FAX number)* IF APPLICABLE
145 Brandywine Parkway West Chester, PA 19380-4245	

PRODUCT DESCRIPTION

NEW DRUG OR ANTIBIOTIC APPLICATION NUMBER, OR BIOLOGICS LICENSE APPLICATION NUMBER (If previously issued) NDA 20-747

ESTABLISHED NAME (*e.g., Proper name, USP/USAN name*)	PROPRIETARY NAME (*trade name*) IF ANY
oral transmucosal fentanyl citrate, OTFC	Actiq

CHEMICAL/BIOCHEMICAL/BLOOD PRODUCT NAME (*if any*): N-(1-phenethyl-4-piperidyl) propionanilide citrate (1:1)
CODE NAME (*if any*):

DOSAGE FORM	STRENGTHS	ROUTE OF ADMINISTRATION
solid, compressed matrix	200, 400, 600, 800, 1200, 1600 ug	oral transmucosal

(PROPOSED) INDICATION(S) FOR USE:
Actiq is indicated only for the management of breakthrough cancer pain in patients with malignancies who are already receiving and who are tolerant to opioid therapy for their underlying persistant cancer pain

APPLICATION INFORMATION

APPLICATION TYPE *(check one)*
☒ NEW DRUG APPLICATION (21 CFR 314.50) ☐ ABBREVIATED NEW DRUG APPLICATION (ANDA, 21 CFR 314.94)
☐ BIOLOGICS LICENSE APPLICATION (21 CFR Part 601)

IF AN NDA, IDENTIFY THE APPROPRIATE TYPE ☒ 505 (b) (1) ☐ 505 (b) (2)

IF AN ANDA, OR 505(b)(2), IDENTIFY THE REFERENCE LISTED DRUG PRODUCT THAT IS THE BASIS FOR THE SUBMISSION
Name of Drug — Holder of Approved Application

TYPE OF SUBMISSION *(check one)*
☐ ORIGINAL APPLICATION ☐ AMENDMENT TO A PENDING APPLICATION ☐ RESUBMISSION
☐ PRESUBMISSION ☐ ANNUAL REPORT ☐ ESTABLISHMENT DESCRIPTION SUPPLEMENT ☐ EFFICACY SUPPLEMENT
☐ LABELING SUPPLEMENT ☐ CHEMISTRY, MANUFACTURING AND CONTROLS SUPPLEMENT ☒ OTHER

IF A SUBMISSION OR PARTIAL APPLICATION, PROVIDE LETTER OF DATE OF AGREEMENT TO PARTIAL SUBMISSION: ____

IF A SUPPLEMENT, IDENTIFY THE APPROPRIATE CATEGORY ☐ CBE ☐ CBE-30 ☐ Prior Approval (PA)

REASON FOR SUBMISSION 17th RMP Quarterly Report

PROPOSED MARKETING STATUS *(check one)* ☒ PRESCRIPTION PRODUCT (Rx) ☐ OVER THE COUNTER PRODUCT (OTC)

NUMBER OF VOLUMES SUBMITTED 1 — THIS APPLICATION IS ☒ PAPER ☐ PAPER AND ELECTRONIC ☐ ELECTRONIC

ESTABLISHMENT INFORMATION (Full establishment information should be provided in the body of the Application.)
Provide locations of all manufacturing, packaging and control sites for drug substance and drug product (continuation sheets may be used if necessary). Include name, address, contact, telephone number, registration number (CFN), DMF number, and manufacturing steps and/or type of testing (e.g. Final dosage form, Stability testing) conducted at this site. Please indicate whether the site is ready for inspection or, if not, when it will be ready.

Please see attached

Cross References (list related License Applications, INDs, NDAs, PMAs, 510(k)s, IDEs, BMFs, and DMFs referenced in the current application)

DMF 10128 Fentanyl Citrate
DMF 13048 Holder/Handle resin
DMF 7273 Blister peel-push lidding
DMF 819 Artificial berry flavor
DMF 3764 Blister roll stock
IND 27,428 Oral Tansmucosal Fentanyl (OTFC)
NDA 20-195 Fentanyl Oralet (Oral Transmucosal Fentanyl Citrate) 100, 200, 300, 400 ug fentanyl base

	This application contains the following items. *(Check all that apply)*
	1. Index
	2. Labeling (check one) ☐ Draft Labeling ☐ Final Printed Labeling
	3. Summary (21 CFR 314.50 (c))
	4. Chemistry section
	A. Chemistry, manufacturing, and controls information (e.g., 21 CFR 314.50(d)(1), 21 CFR 601.2)
	B. Samples (21 CFR 314.50 (e)(1); 21 CFR 601.2 (a)) (Submit only upon FDA's request)
	C. Methods validation package (e.g., 21 CFR 314.50(e)(2)(i); 21 CFR 601.2)
	5. Nonclinical pharmacology and toxicology section (e.g., 21 CFR 314.50(d)(2), 21 CFR 601.2)
	6. Human pharmacokinetics and bioavailability section (e.g., 21 CFR 314.50(d)(3); 21 CFR 601.2)
	7. Clinical Microbiology (e.g., 21 CFR 314.50(d)(4))
	8. Clinical data section (e.g., 314.50(d)(5); 21 CFR 601.2)
	9. Safety update report (e.g., 21 CFR 314.50(d)(5)(vi)(b); 21 CFR 601.2)
	10. Statistical section (e.g., 21 CFR 314.50(d)(6); 21 CFR 601.2)
	11. Case report tabulations (e.g., 21 CFR 314.50(f)(1), 21 CFR 601.2)
	12. Case reports forms (e.g., 21 CFR 314.50 (f)(2); 21 CFR 601.2)
	13. Patent information on any patent which claims the drug (21 U.S.C. 355 (b) or (c))
	14. A patent certification with respect to any patent which claims the drug (21 U.S.C. 355 (b)(2) or (j)(2)(A))
	15. Establishment description (21 CFR Part 600, if applicable)
	16. Debarment certification (FD&C Act 306 (k)(1))
	17. Field copy certification (21 CFR 314.50 (k)(3))
	18. User Fee Cover Sheet (Form FDA 3397)
	19. Financial Information (21 CFR Part 54)
X	20. OTHER *(Specify)* 17th RMP Quarterly Report

CERTIFICATION

I agree to update this application with new safety information about the product that may reasonably affect the statement of contraindications, warnings, precautions, or adverse reactions in the draft labeling. I agree to submit safety update reports as provided for by regulation or as requested by FDA. If this application is approved, I agree to comply with all applicable laws and regulations that apply to approved applications, including, but not limited to the following:

1. Good manufacturing practice regulations in 21 CFR Parts 210, 211 or applicable regulations Parts 606, and/or 820.
2. Biological establishment standards in 21 CFR Part 600.
3. Labeling regulations in 21 CFR Parts 201, 606, 610, 660 and/or 809.
4. In the case of a prescription drug or biological product, prescription drug advertising regulations in 21 CFR 202.
5. Regulations on making changes in application in FD&C Act Section 506A, 21 CFR 314.71, 314.72, 314.97, 314.99, and 601.12.
6. Regulations on Reports in 21 CFR 314.80, 314.81, 600.80, and 600.81.
7. Local, state and Federal environmental impact laws.

If this application applies to a drug product that FDA has proposed for scheduling under the Controlled Substances Act I agree not to market the product until the Drug Enforcement Administration makes a final scheduling decision.

The data and information in this submission have been reviewed and, to the best of my knowledge are certified to be true and accurate.

Warning: a willfully false statement is a criminal offense, U.S. Code, title 18, section 1001.

SIGNATURE OF RESPONSIBLE OFFICIAL OR AGENT	TYPED NAME AND TITLE	DATE
Carol S. Marchione	Carol S. Marchione Senior Director, Regulatory Affairs	09/24/03

ADDRESS (*Street, City, State, and ZIP Code*)	Telephone Number
145 Brandywine Parkway West Chester, PA 19380-4245	(610) 738-6237

Public reporting burden for this collection of information is estimated to average 24 hours per response, including the time for reviewing instructions, searching existing data sources, gathering and maintaining the data needed, and completing and reviewing the collection of information. Send comments regarding this burden estimate or any other aspect of this collection of information, including suggestions for reducing this burden to:

Department of Health and Human Services
Food and Drug Administration
CBER, HFM-99
1401 Rockville Pike
Rockville, MD 20852-1448

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FORM FDA 356h (4/00) PAGE 2

Establishment Information for Form FDA 356h:

Drug Substance: Fentanyl Citrate, USP

DMF 10128

Administrative address:
Mallinckrodt Inc.
675 McDonnell Boulevard
PO Box 5840
St. Louis, Missouri 63134
USA

Manufacturing site:
Mallinckrodt Inc.
3600 North 2nd Street
St. Louis, Missouri 63147
USA

Contact: Mr. Charles H. Smith
Responsible Agent
314-654-6128

Drug Product: Actiq® (Oral Transmucosal Fentanyl Citrate)

Cephalon, Inc.
4745 Wiley Post Way
Salt Lake City, Utah 84116, USA.
Contact: Mr. Charles M. Barr
Senior Director, Manufacturing Operations
and General Manager
Salt Lake Division
801-595-1405

CONFIDENTIAL INFORMATION

Contains trade secret and/or confidential information which is the property of CEPHALON, INC. As provided by 21 CFR § 20.61, DO NOT DISCLOSE to the public.

Actiq® Risk Management Program

17th Quarterly Report

(April 1, 2003 through June 30, 2003)

Actiq Surveillance and Monitoring Program (Sections 8.0 and 9.0)

8.0 Surveillance Goals and Activities

8.1 Direct Patient Feedback

8.1.1 Chain Pharmacy Call Back System

Starting in 1999, Cephalon instituted a pharmacy call back system with Walgreen's Pharmacy to solicit information regarding the effectiveness of the Actiq Risk Management Program utilizing a telephone questionnaire.

The call back system directly queries Actiq patients in regard to aspects of patient selection and child safety. This program was designed to capture "real time" trends of inappropriate patient selection and child safety issues during the first year of sales. This program currently remains in place, with participating (partner) pharmacies presently limited to Walgreen's.

As of June 30, 2003, Cephalon, Inc. has received data from 7068 patient interviews conducted since product launch, 963 of the interviews were performed this quarter. The cumulative results are summarized in Appendix 1.

***Key findings to date include*:**

1) Approximately 27.4% of prescribers were compliant with current dosing recommendations (starting dose = 200 mcg) for patients initiating therapy with Actiq.
2) The majority of respondents (95.7%) were receiving chronic opioid therapy when Actiq was prescribed.
3) The majority of respondents (84%) received the appropriate safety messages via their physicians or pharmacists.
4) The majority of respondents (58.6%) reported no children were in the home or had access to the home.
5) Approximately 23.3% of the survey respondents received the Actiq Welcome Kit when the product was dispensed.
6) Approximately 1.9% of the respondents utilized the Actiq Welcome Kit for storage of the Actiq units. The majority of the respondents (52%%) utilized either a locked cabinet or the home medicine cabinet.
7) Trash receptacles were the primary site of disposal for both finished and partially consumed Actiq units. Approximately 37.5% of the respondents followed the disposal instructions for partially consumed units, compared with 36.2% of the respondents who inappropriately disposed of the units in the trash.

8) Of the 2564 respondents who reported that they had children in the home or with access to the home, 850 (33%) reported disposing of partially consumed units in the trash.

8.2 Prescription Monitoring

8.2.1 NDC Source Prescriber Audit

Data from the NDC Source Prescriber audit show that none of the non-targeted physician specialties exceeded 15% of the total prescriptions during 2Q03.

8.2.2 IMS National Disease and Therapeutic Index (NDTI)

Data from IMS National Disease and Therapeutic Audit (NDTI) showing the uses of Actiq are shown in Appendix 2.

8.2.3 Wholesaler Data

Quarterly wholesaler-to-retail shipment data for the 2nd Quarter 2003 has been forwarded to the Cephalon Pain Care Specialists for follow-up during their regular field activities.

8.3 Adverse Events

8.3.1 Cephalon Standard Operating Procedure

Cephalon, Inc. has established procedures to guide processing of all adverse drug experience (ADE) reports.

A toll-free number that may be accessed 24 hours a day is available to receive ADE reports. Reports are logged into the Global Product Safety database, regardless of source, and processed according to Cephalon procedures and guidelines. Global Product Safety is responsible for oversight of the processing of ADE reports and for briefing senior management as indicated.

The processing of ADE reports is guided by a Standard Operating Procedure summarized below.

a) Each ADE report is reviewed to establish the initial regulatory report classification, the reported ADE term(s), and to assess the report for seriousness, relatedness, and expectedness, based on criteria outlined in 21 CFR 314.80. In addition, for ADE reports associated with Actiq, these findings are then reviewed to determine reportability in accordance with the Special Safety Commitments for Actiq (see Section 8.3.2).

b) The reporter is contacted by Global Product Safety personnel in a timely fashion should additional information be required.

8.3.2 Special Safety Commitments

In addition to the requirements for 15-Day Alert Reports under 21 CFR 314.80, the following events also require expedited reporting (regardless of source – spontaneous, study or literature):

- **Any unintended pediatric exposure**, whether or not serious and whether or not unexpected,
- **Any serious adverse drug experience** which is determined to occur in the **context of diversion** (i.e., use by an individual other than for whom it was prescribed), whether or not considered unexpected,
- **Any serious adverse drug experience** which is determined to occur in the **context of "off-label use"** (i.e., that is used outside of the approved indication for Actiq) whether or not considered unexpected.

The following table summarizes all reports received during this reporting period for Actiq, including all reports meeting the criteria outlined in the Special Safety Commitments for Actiq.

***Actiq* Product Experience Reports** [1]

Quarter ending 30 June 2003

Time Period	Total No. of Cases	Off-Label Prescribing No Usage	Off-Label Prescribing and Usage	Serious ADE Related to Diversion or Off-Label Use	Unintended Pediatric Exposure	Serious ADE related to On-Label Use
April 2003	40	0	16** 15***	1	2	0
May 2003	49	2	24** 21***	3	2	0
June 2003	44	3	24** 17***	2	0	0

[1]See Appendix 3 for a cumulative tabulation of cases to date.
Table excludes ex-U.S. cases that may represent off-label use.
**Appropriate physician follow-up letter was sent.
*** Physician's name was not revealed; therefore, follow-up letter could not be sent.

A total of 133 spontaneous cases were registered in April, May and June 2003. Of these cases, four involved pediatric exposures (Case # US010853, US010885, US010981, US011003). There was one additional case of a fatal suspected drug overdose involving a 16-year old female with a history of drug abuse (Case #US010903). This report was classified as a serious ADE that occurred in the context of diversion. Additionally, there were five other cases that involved serious ADEs related to

diversion or off-label use. Thus, 10 cases were determined to meet the expedited reporting criteria during the reporting period (Table I).

Table I. Actiq RMP ADE Reports Submitted as 15-Day Alerts for Quarter Ending 30 June 2003

Event Type	Cephalon MCN*	Submission Date
Pediatric Exposures		
	US010853	18 Apr 2003
	US010885	25 Apr 2003
	US010981	22 May 2003
	US011003	03 Jun 2003
SAE Related to Diversion or Off-Label Use	US010903	1 May 2003
	US010944	19 May, 23 Jun 2003
	US011061	20 Jun 2003
	US011035	12 Jun 2003
	US011087	02 Jul 2003
	US011012	30 May 2003
* MCN=manufacturer's control number		

The spontaneous expedited ADE reports received for Actiq during the reporting period are summarized by reporting category below.

Expedited ADEs under Actiq Risk Management Program

Accidental Pediatric Exposures

US010853

05-Apr-03: This case was assessed by Cephalon as an important medical event.

A consumer report received from the father of a 9-month old infant female who retrieved one Actiq (oral transmucosal fentanyl citrate) 1600mcg lozenge from the mother's purse. The lozenge was found in the child's mouth. When the mother picked up the child, her eyes rolled back in her head, she was "purple", limp and breathing irregularly. The mother initiated artificial respiration, 911 was activated, and the infant was transported by ambulance to the emergency department (ED). In the ED, the baby was given "medicine to counteract" the effects of Actiq. All symptoms resolved within three hours and the baby was discharged to home with no residual effects. No further information is available.

Corporate comment: The consumer reported events of "eyes rolled back, purple and limp" were assessed s symptoms of respiratory depression which is expected in non-opioid tolerant patients exposed to high doses of fentanyl citrate.

Additional note: It is unlikely that a 9-month old infant could open a sealed pouch, however, no additional information is available regarding this case.

US010885

12-Apr-03: A consumer report received from the mother of a 2 1/2 year old male, weighing 30 pounds, who was accidentally exposed to a partially consumed Actiq (oral transmucosal fentanyl citrate) 800mcg lozenge. The child's mother used the lozenge and laid it down. The child picked up the lozenge and placed it in his mouth for approximately 30 seconds. At the time of the call to the Poison Control Center (approximately 45 - 60 minutes after the exposure), the child was asymptomatic. The child was subsequently taken to a local hospital where he was noted to be asymptomatic and released to home.

US010981

12-May-03: A consumer report received regarding the accidental ingestion of an Actiq (oral transmucosal fentanyl citrate) lozenge by a 19-month-old male child. The grandmother, for whom the Actiq is prescribed, reports that she normally uses the Welcome Kit and lockbox to store the Actiq units, but on 12-May-03 she removed an Actiq 600mcg lozenge from the wrapper and placed it on a shelf. A short time later, the child was observed with the unit in his mouth, the lozenge appeared to have been chewed and approximately 1/8 remained on the handle. Following ingestion, the child remained awake and playing, however, he appeared to be sleepy, scratching at his nose, and yawning. Emergency services were notified and, on arrival, established an intravenous access prior to transporting the child to a hospital emergency room (ER). In the ER, no treatment was administered nor were laboratory tests performed. Respiratory status was monitored by pulse oximetry and was reported to be within normal range. After 5 hours of observation the child, having remained in stable condition, was discharged to home.

US011003

18-May-03: A consumer report received regarding a 4-year-old male child. The father, who used Actiq (oral transmucosal fentanyl), reported that he had noted (the day prior to this call) that the foil wrapper on a 600ug unit had been cut open with scissors. Although, it appeared there was no significant or noticeable amount missing from the lozenge, he suspected that the 4-year-old had possibly been exposed to the lozenge. The father observed the child and reported that he had acted tired and sleepy, rubbing around his nose and pulling his ears. The father continued to monitor the child, while he slept, over the next ten hours and noted no other adverse effects. The following day the child was reported to be a little less active than usual. The father was advised that, due to the potential for respiratory depression, in the event of an accidental exposure, emergency services should be notified and the child should be evaluated by a physician. No further information is available.

Serious ADEs Associated With Diversion

US010903

18-Apr-03: Report received from a sales representative regarding a 16-year-old female with a history of drug abuse, who died from an apparent drug overdose on 15-Apr-03 at a party. The death was also reported in the local newspaper. Initial investigation revealed "she overdosed on morphine-laced lollipops", but a local television broadcast noted Actiq (oral transmucosal fentanyl citrate) may have played a part in the girl's death. Toxicology results were not available.

23-Apr-03: Additional information received from the investigating officer. The officer stated that there is some concern that the deceased may have consumed an 800mcg Actiq lozenge with other drugs that were found at the site [OxyContin (oxycodone), Xanax (alprazolam), Ecstasy] and/or alcohol. Four empty Actiq 800mcg wrappers and handles were found in the home where the girl expired. The officer noted that a boy had come to the party with a full box of Actiq 800mcg units. Toxicology results are pending.

Additional note: To date, attempts to obtain the toxicology results have been unsuccessful.

US010944

01-May-03: A police detective reported that "someone obtained Actiq (oral transmucosal fentanyl citrate) illegally."

09-May-03: Additional information was received from the police detective regarding a 20-year-old female who expired possibly related to consuming an Actiq (oral transmucosal fentanyl citrate) lozenge. The detective noted that a 1600mcg Actiq wrapper was found at the scene. Toxicology results are pending. No further details were received.

09-Jun-03: On follow up, the detective reported that the investigation was ongoing, however, preliminary results indicated that Actiq was not involved. The detective also stated that no further information would be released until the investigation was concluded.

Serious ADEs Associated With Off-Label Use

US011035

28-May-03: A consumer report received regarding a 70-year-old male with a history of depression. In May-02, the patient initiated Actiq (oral transmucosal fentanyl citrate) therapy, for back pain, and shortly thereafter exhibited bizarre behaviors and experienced hallucinations. The patient also reported intermittent fevers over the past year. Concomitant medications included Duragesic (fentanyl) patches and Ativan (lorazepam). In May-03, the patient was briefly hospitalized with a diagnosis of fever. Actiq therapy was discontinued in May-03 and the Duragesic dose was increased. The reporter stated that following the

discontinuation of Actiq therapy, the events of bizarre behavior and hallucinations intensified and, additionally, the patient developed memory loss, aggressiveness and paranoia.

US011087

10-Jun-03: A report received from a consumer regarding a 45-year-old female. On 10-Jun-03, the patient initiated Actiq (oral transmucosal fentanyl citrate) therapy for pain associated with rheumatoid arthritis. The patient used one 200mcg lozenge and two hours later experienced nausea and vomiting. The reporter indicated that the patient had taken Actiq on an empty stomach. Actiq therapy was subsequently discontinued and the events resolved.

19-Jun-03: Follow up received from the consumer on 19-Jun and 24-Jun-03 indicated that on 11-Jun-03, fifteen minutes after ingestion of an Actiq lozenge, the patient began to experience dry heaves and vomiting which continued all day and she was unable to eat. The patient was observed to be hardly breathing and was admitted to the hospital. The patient was treated with intravenous fluids and her dose of Duragesic (fentanyl patch) was decreased from 50mcg/hr to 25mcg/hr. A chest x-ray was performed but the results were unknown. The patient was discharged from the hospital one day later with the dry heaves and vomiting resolved and her appetite improving. The patient also reported having lost weight (from 101 to 74lbs) since initiating Actiq therapy. Actiq therapy was discontinued on 11-Jun-03 and restarted on 23-Jun-03.

US011012

16-May-03: A consumer report received from a 38-year-old female who initiated Actiq (oral transmucosal fentanyl citrate) therapy 200 to 600mcg up to fifteen times daily for post-operative pain. The patient reported that she has become addicted to Actiq and, under the care of a physician and psychologist, has been able to decrease her usage to 200mcg eight times daily and then to 200mcg six times daily. When she attempts to further decrease the dose she experiences "shakes and feels as if she is jumping out of her skin". The patient also indicated that a component of her addiction is the oral gratification/satisfaction derived from Actiq. No further information is available.

US011061

06-Jun-03: Report received from Johnson and Johnson (NSADSS2003021050), regarding a 40-year-old male with a history of depression and intractable facial pain secondary to a mandibular fracture. On 15-Sep-02, the patient filled a prescription for Actiq (oral transmucosal fentanyl citrate), 800mcg, and the same day was found dead in his car with a tourniquet on his arm and a syringe in his right hand. Suspect medication also included Duragesic (fentanyl TTS), 75mcg/hour, 1 patch every 72 hours. However, no patches were found on the patient's body. An autopsy revealed a blood level of 0.4mg of fentanyl; no fentanyl was found in the gastric contents. Cause of death was listed as acute fentanyl intoxication.

Corporate comment: The mechanism by which fentanyl was absorbed into the body has not been confirmed. There was no reported evidence of Actiq found with the deceased, however, the possibility that Actiq was used by another route or mechanism cannot be excluded.

Clinical Trial Serious Adverse Events (SAEs)

Currently, there are no ongoing clinical trials being conducted with Actiq.

8.3.3 Non-Expedited RMP Cases

In addition to the expedited reporting requirements under the Special Safety Commitment, cases of diversion not associated with ADEs are described below:

US010839 (Diversion)

01-Apr-03: A report received from a police lieutenant (Narcotics Division) regarding the arrest on 31-Mar-03 of a suspect accused of selling 17 Actiq (oral transmucosal fentanyl citrate) 800mcg lozenges to an undercover police officer. The officer reported that the suspect stated that his supplier had a large quantity of Actiq, "over 3,000 units" and that approximately 600 units were sold over the past three days. The officer reported that the units are being "crushed and injected like heroin."

10-Apr-03: Follow-up information received from a police investigative report indicated one male was arrested for selling Actiq and another male was arrested for conspiracy to traffic Actiq. The Actiq lozenges were recovered by the police officer.

8.3.4 Literature Monitoring

There were no pediatric or serious adverse events noted in the literature search for the reporting period.

8.4 Poisoning and Overdose

Reports in this section are derived from Poison Control calls to our toll-free number currently monitored by Rocky Mountain Poison and Drug Center (RMPDC) and the Toxic Exposure Surveillance System (TESS). TESS reports all contacts to U.S. Poison Control Centers.

8.4.1 Central 1-800 Poison Control Number

RMPDC Case Summary Report‡

Date of Call	RMPDC Case #	Cephalon Case #	State	History
04/05/03	856256	010853	CA	ADE: **Pediatric Exposure**
04/12/03	859755	010885	UT	**Pediatric Exposure:** Asymptomatic
04/18/03	862753	010903	FL	**Diversion associated with serious ADE**
05/12/03	875653	010981	UT	ADE: **Pediatric Exposure**
05/16/03	877876	011012	NY	**Serious ADE associated with Off-Label Use**
05/18/03	878997	011003	CA	ADE: **Pediatric Exposure**

Refer to Section 8.3.2, Special Safety Commitments, for case summaries.
‡Table excludes calls related to non-expedited ADEs and animal exposures

8.4.2 Toxic Exposure Surveillance System (TESS)

Toxic Exposure Surveillance System (TESS) data are compiled by the American Association of Poison Control Centers (AAPCC) in cooperation with the majority of US poison centers. The cumulative AAPCC database (annual reports available at www.aapcc.org/poison1.html) now contains 31.4 million human poison exposure cases. The most recent annual report was compiled in 2001 and the identified Actiq exposures were described in the 14th Actiq RMP Quarterly Report. At the time of this report, there have been no subsequent TESS reports issued.

8.5 Abuse

Information regarding abuse of Actiq is derived from spontaneous ADE reports and information received from the following source:

8.5.1 Drug Abuse Warning Network (DAWN)

The Drug Abuse Warning Network (DAWN) is a voluntary, national data collection system that gathers information on substance abuse that results in visits to hospital emergency departments (EDs) in the continental U.S.

The data collection methodology requires that each drug abuse patient who visited a participating DAWN ED meet certain criteria. To be included in DAWN, the patient must be between the ages of 6 and 97 and meet the following four criteria:

- The patient was treated in the hospital's ED;
- The patient's presenting problem(s) was induced by or related to drug use, regardless of when the drug use occurred;
- The episode involved the use of an illegal drug or the use of a legal drug or other chemical substance contrary to directions; and

- The patient's reason for using the substance(s) was dependence, suicide attempt or gesture, and/or psychic effects.

As previously noted, DAWN does not publish estimates for particular brands and due to the lack of specificity provided by the DAWN data, it is not possible to identify mentions which might have specifically involved Actiq use. The findings from the most recent DAWN report were summarized in the 16th Actiq RMP Quarterly Report. At the time of this report, there have been no subsequent published DAWN reports providing estimates of fentanyl abuse. All DAWN reports are published on the National Clearinghouse for Alcohol and Drug Information website ((www.samhsa.gov/oas/dawn.html).

8.6 Promotional Message Audit

As part of our Risk Management Program, we are required to provide detail recall information twice annually. We use a company called Strategic Business Research (SBR) to conduct a survey of 50 physicians on a semiannual basis. Please see Appendix 4 for a report assessing detail recall information covering the period from January 1, 2003 through June 30, 2003.

9.0 Intervention

Data used to evaluate current trends and interventions are derived from the following sources and are summarized in this report:

1) Adverse Drug Experiences (see Section 8.3.2; Appendix 3)
2) Sales Force: Reports of ADEs and/or off-label use reported by sales representatives during the reporting period
3) Patient reports, sales information (section 8.6; Appendix 2, Appendix 4) or other reliable sources reported to the Cephalon Global Product Safety and Medical Affairs Departments.
4) Chain Pharmacy Call-Back System (Section 8.1.1; Appendix 1)

9.1 Off-Label Usage

9.1.1 Individual Prescribers

When reports containing any mention of off-label usage of Actiq are received where the prescriber contact information is known, the following procedures are followed:

1) Initial instance of off-label use: A letter from Global Product Safety is mailed to the prescriber emphasizing the approved indication, appropriate patient selection, and key safety messages. An electronic copy of the letter is stored in the Global Product Safety electronic files.

2) Repeat instance of off-label use by the same prescriber: An e-mail notification is sent to designated Cephalon employees in Sales and Marketing, Regulatory Affairs, and Medical Affairs for appropriate action as outlined in the Risk Management Plan. A copy of the email message is inserted into the case file.

9.2 Accidental Ingestion

Any unintended pediatric accidental ingestion is handled as a serious ADE. During this quarter, reports of unintended pediatric exposure represented approximately 3% of all Actiq ADE reports (see Section 8.3.2). Based upon the information provided at the time of the report, all of the reported pediatric exposures received this quarter resulted from parental or caregiver inattention or improper storage/disposal of Actiq. However, an increased in reporting frequency was not seen when compared to the quarter ending 31 March 2003.

Cephalon, Inc. continues to work towards our goal of preventing unintended exposure to Actiq. Our primary efforts are aimed at informing patients, prescribers, and pharmacists of the important safety messages for Actiq, with special emphasis on child safety and the proper storage and disposal of Actiq. All Cephalon sales representatives are informed of these key safety messages during sales training, and the sales force is encouraged to review these key messages, including the use of the Actiq Welcome Kit, with pharmacists, prescribers and other medical office staff.

Appendix 1

Chain Pharmacy Call Back System (from Section 8.1.1)

Under this program, patients who receive an *Actiq* prescription at a participating pharmacy will receive a follow-up phone call by a company pharmacist. It should be noted that with each survey the patient and/or caregiver is reminded that:

- *Actiq* is only for breakthrough cancer pain for those patients who are taking chronic opioids.
- *Actiq* must be kept in a locked space where children do not have access.
- The items in the *Actiq* Welcome Kit should be used to protect children in the home.
- A toll-free number (888-818-4113) is available for patient questions and to request a Welcome Kit.

As of **June 30, 2003**, Cephalon Inc. has received data from 7068 patient interviews. These cumulative results are summarized below. Answers not provided have been labeled "N/A" and "% total" refers to the total number of completed surveys. In some cases, more than one response was given for each question. Therefore, percentages may not constitute 100% in all instances.

1. Did the patient receive an *Actiq* Welcome Kit?

		% total (n= 7067)	%respondents (n= 6827)
Yes	1590	(22.5%)	(23.3%)
No	5237	(74.1%)	(76.7%)
N/A*	240	(3.4%)	

2. Was the patient already on a strong opioid when they received the *Actiq* prescription?

		% total (n=7065)	%respondents (n= 6755)
Yes	6463	(91.5%)	(95.7%)
No	292	(4.1%)	(4.3%)
N/A*	310	(4.4%)	

3. Was the patient or caregiver provided with the appropriate safety messages (by the pharmacist or physician)?

		% total (n=6975)	%respondents (n= 6557)
Yes	5507	(78.9%)	(84%)
No	1050	(15.0%)	(16%)
N/A*	418	(6%)	

Starting Dose		% total (n=6944)	% respondents (n=6273)
200 mcg	1721	(24.8%)	(27.4%)
400 mcg	2972	(42.8%)	(47.4%)
600 mcg	727	(10.5%)	(11.6%)
800 mcg	666	(9.6%)	(10.6%)
1200 mcg	94	(1.4%)	(1.5%)
1600 mcg	93	(1.3%)	(1.5%)
N/A*	671	(9.6%)	

Current Dose**		% total N=7060	% respondents N=6811
200 mcg	1956	(27.7%)	(28.7%)
400 mcg	2947	(41.7%)	(43.3%)
600 mcg	792	(11.2%)	(11.6%)
800 mcg	813	(11.5%)	(11.9%)
1200 mcg	154	(2.2%)	(2.2%)
1600 mcg	149	(2.1%)	(2.2%)
N/A*	249	(3.5%)	

*Not answered.
**More than one choice may be selected.

4. Are there any children in the home or with access to the home?

		%total N=7064	%respondents N=6196
Yes	2564	(36.3%)	(41.4%)
No	3632	(51.4%)	(58.6%)
N/A*	868	(12.3%)	

5. How is the patient or caregiver storing and disposing of the product?

Storage**		% total N=6435
Welcome Kit	121	(1.9%)
Medicine cabinet	1124	(17.4%)
Locked cabinet	1583	(24.6%)
No special storage	738	(11.5%)
Other or N/A*	2869	(44.6%)

Disposal for Finished Units **		% total N= 7541
Throw it in the trash	4964	(65.8%)
Put under hot water and then in the trash	1508	(20%)
Using the safety container from the Welcome Kit	178	(2.3%)
Cut the medicine off so that it falls into the toilet	78	(1%)
Other or N/A*	813	(10.8%)

Disposal for Unfinished Units **		% total N=7437
Throw it in the trash	2056	(36.2%)
Put under hot water and then in the trash	1984	(37.5%)
Using the safety container from the Welcome Kit	94	(1.3%)
Cut the medicine off so that it falls into the toilet	183	(2.5%)
Always finishes	1008	(13.5%)
Other or N/A*	2112	(28.4%)

* Not answered.
** More than one choice may be selected.

Appendix 2

IMS National Disease and Therapeutic Index (NDTI)

Variable : P-Default Measure (Thousands)

	Q03/2000 (Jul-Sep)	Q04/2000 (Oct-Dec)	Q01/2001 (Jan-Mar)	Q02/2001 (Apr-Jun)	Q03/2001 (Jul-Sep)	Q04/2001 (Oct-Dec)
Actiq CEH 99/04	2	3	---	---	2	6
7809 Chronic Pain Syndrome	---	---	---	---	---	---
3469 Migraine Unspecified	---	---	---	---	---	---
1541 Mal Neo of Rectum	2	---	---	---	---	---
1579 Mal Neo Pancreas Uns	---	---	---	---	---	1
1629 Mal Neo Bronch+Lung Unsp	---	---	---	---	---	2
1749 Mal Neo Fem Breast Unsp	---	---	---	---	---	3
1850 Malig Neo of Prostate	---	---	---	---	---	---
2030 Multiple Myeloma	---	3	---	---	---	---
3559 Mononeuritis Unsp Site	---	---	---	---	2	---
7140 Rheumatoid Arthritis Nec	---	---	---	---	---	---
7231 Cervicalgia	---	---	---	---	---	---
7245 Backache Unspec	---	---	---	---	---	---
7840 Headache	---	---	---	---	---	---

Appendix 2 (continued)

IMS National Disease and Therapeutic Index (NDTI)

Variable : P-Default Measure (Thousands)

	Q01/2002 (Jan-Mar)	Q02/2002 (Apr-Jun)	Q03/2002 (Jul-Sep)	Q04/2002 (Oct-Dec)	Q01/2003 (Jan-Mar)	Q02/2003 (Apr-Jun)
Actiq CEII 99/04	3	---	---	9	3	6
7809 Chronic Pain Syndrome	---	---	---	---	---	4
3469 Migraine Unspecified	---	---	---	---	2	2
1541 Mal Neo of Rectum	---	---	---	---	---	---
1579 Mal Neo Pancreas Uns	---	---	---	---	1	---
1629 Mal Neo Bronch-Lung Unsp	---	---	---	---	---	---
1749 Mal Neo Fem Breast Unsp	1	---	---	---	---	---
1850 Malig Neo of Prostate	1	---	---	---	---	---
2030 Multiple Myeloma	---	---	---	---	---	---
3559 Mononeuritis Unsp Site	---	---	---	---	---	---
7140 Rheumatoid Arthritis Nec	---	---	---	1	---	---
7231 Cervicalgia	---	---	---	4	---	---
7245 Backache Unspec	---	---	---	4	---	---
7840 Headache	---	---	---	1	---	---

Appendix 3

Actiq Product Experience Reports

This table provides a comprehensive tabulation of *Actiq* Product Experience Reports to date (i.e., for the period covering 1 April 1999 through June 30, 2003). Also included are any cases involving serious Adverse Drug Experiences (ADEs) and/or off-label usage.

Time Period	Total No. of Cases§	Off-Label Prescribing No Usage	Off-Label Prescribing and Usage	Serious ADE Related to Diversion or Off-Label Use	Pediatric Exposure	Serious ADE related to On-Label Use
April/May 1999	3	1*	2**	0	0	0
June 1999	3	1*	0	0	0	2
July 1999	1	0	1**	0	0	0
August 1999	1	0	1***	0	0	0
September 1999	1	0	0	0	0	1
October 1999	2	0	1***	0	0	1
November 1999	4	0	1**	0	0	3
December 1999	6	0	2***	0	0	4
January 2000	0	0	0	0	0	0
February 2000	1	0	1**	0	0	0
March 2000	6	0	3** 1***	0	0	2
April 2000	10	0	4** 3***	0	0	3
May 2000	7	0	3** 2***	0	0	2
June 2000	1	0	1***	0	0	0
July 2000	9	1** 1***	1** 1***	0	0	5
August 2000	5	0	1** 1***	0	1	2
September 2000	6	0	2**	0	0	4
October 2000	5§	0	2**	1	0	1
November 2000	2§	0	0	0	0	1
December 2000	8§	0	0	0	1	6

Appendix 3 (Continued)

Time Period	Total No. of Cases‡	Off-Label Prescribing No Usage	Off-Label Prescribing and Usage	Serious ADE Related to Diversion or Off-Label Use	Pediatric Exposure	Serious ADE related to On-Label Use
January 2001	4§	0	2*** 1**	0	0	1
February 2001	3§	0	3**	0	0	0
March 2001	7§	0	2*** 5**	0	0	0
April 2001	8	0	2*** 2**	0	0	1 1†
May 2001	9	0	2** 4***	0	0	1 1†
June 2001	10	0	1*** 7**	1	1	0
July 2001	10	0	8** 0***	0	0	0
August 2001	11	0	7** 2***	1	0	0
September 2001	11	0	5** 1***	1	0	0
October 2001	8	0	3** 2***	1	1	1
November 2001	6	0	3** 1***	0	0	0
December 2001	7	0	1** 2***	0	0	1

Appendix 3 (Continued)

Time Period	Total No. of Cases‡	Off-Label Prescribing No Usage	Off-Label Prescribing and Usage	Serious ADE Related to Diversion or Off-Label Use	Pediatric Exposure	Serious ADE related to On-Label Use
January 2002	31	1	20** 5***	2	2	1
February 2002	23	0	5** 5***	0	1	4
March 2002	23	0	10** 3***	0	1	1
April 2002	27	1	20** 2***	0	1	3
May 2002	32	0	12** 9***	0	1	2
Jun 2002	26	1	12** 6***	0	1	0
July 2002	39	0	19** 12***	4	1	2
August 2002	42	0	21** 15***	0	0	1
September 2002	40	1	16** 14***	1	1	1
October 2002	45	0	21** 13***	1	0	3
November 2002	28	0	14** 9***	1	1	1
December 2002	36	0	17** 12***	4	0	0
January 2003	36	0	22** 10***	1	0	0
February 2003	50	0	29** 11***	0	2	0
March 2003	45	0	16** 23***	2	3	0
April 2003	40	0	16** 15***	1	2	0
May 2003	49	2	24** 21***	3	2	0
June 2003	44	3	24** 17***	2	0	0

*Pharmacist did not dispense drug because of potential off-label use.
** Appropriate physician follow-up letter was sent.
*** Physician's name was not revealed; therefore, follow-up letter could not be sent.
‡Not included are non-serious, on-label ADEs. † Solicited reports from a Phase 4 trial in progress.
‡Non-Human exposures are no longer classified as product experience reports

Appendix 4

SBR
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Marketing Research and Consulting
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FINAL REPORT

ACTIQ® (oral transmucosal fentanyl citrate)

Detailing Message Tracking Study

Wave V

Prepared for:

Cephalon, Inc.
145 Brandywine Parkway
West Chester, PA 19380-4245

July 24, 2003

I. BACKGROUND

Cephalon currently markets ACTIQ (fentanyl transmucosal system), a product containing the opioid analgesic fentanyl that is designed to control breakthrough cancer pain. ACTIQ is supplied in a formulation that resembles a lollipop, and is ingested in a similar fashion. Given the unique oral transmucosal system of ACTIQ, fentanyl is absorbed rapidly and patients can begin experiencing pain relief in fifteen minutes while taking ACTIQ.

Because of the potential for accidental ingestion and overdose, the Food and Drug Administration (FDA), has required Cephalon to carefully inform physicians of the proper usage, storage, and disposal of ACTIQ. In addition, Cephalon is required to monitor the detailing activity of its sales force in order to show compliance with FDA requirements.

Strategic Business Research, Inc., (SBR), an independent healthcare marketing research and consulting firm, has been contracted by Cephalon to conduct an ongoing survey of physicians regarding the detailing of ACTIQ by Cephalon sales reps.

II. RESEARCH METHODOLOGY

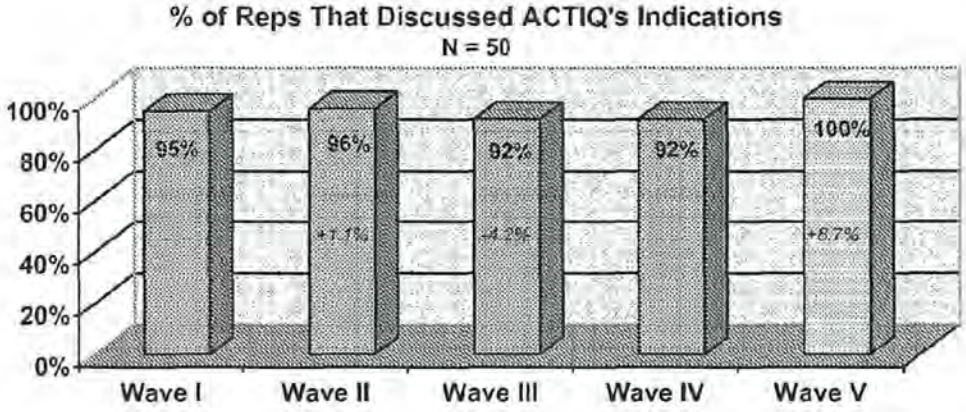
Physicians were recruited from a list provided by Cephalon to SBR that contained pain management specialists and oncologists that had been detailed by Cephalon reps in the six-month period preceding this wave of the research. Participants were contacted randomly and asked to take part in this brief telephone interview. *Completion of the entire questionnaire was contingent upon physicians having prescribed ACTIQ within the six-month period preceding the interview and having been detailed by a Cephalon sales representative at least once during the three months prior to the interview.* The fielding of the research took place between July 11 and July 19, 2003. This was the fifth phase of this project. Previous phases were conducted in August 2001, February 2002, August 2002, and February 2003. This phase included 33 pain management specialists and 17 oncologists, representing a proportionate amount of each specialty given that two-thirds of the supplied list was comprised of pain management specialists.

III. DETAILED FINDINGS

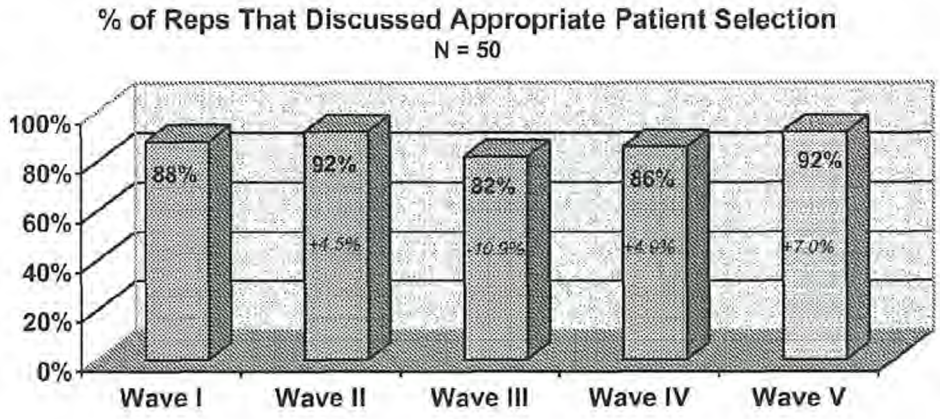
SBR contacted a total of 96 physicians that agreed to participate in this wave of the research. Of these, 53 (55%) had actually prescribed ACTIQ during the six months prior to being contacted. This percentage has substantially improved from the last wave of research in February, where only 39% of physicians contacted claimed to have prescribed ACTIQ in the six months preceding the research. While the true cause of this difference is unknown, there are a variety of factors that could account for this; including an improvement in the quality of the list supplied by Cephalon and/or an event/occurrence/development that served to increase the preponderance of ACTIQ prescribing by physicians.

Of the 53 physicians who had prescribed ACTIQ, only 3 (6%) could not recall having been detailed by a rep promoting ACTIQ in the three-month period preceding the research, and no respondent stated that he/she had definitely not been detailed in that time period. Again, this represents a marked improvement, as the previous wave of this research included 33 respondents who claimed they had not been detailed in the three months prior to the date they were contacted.

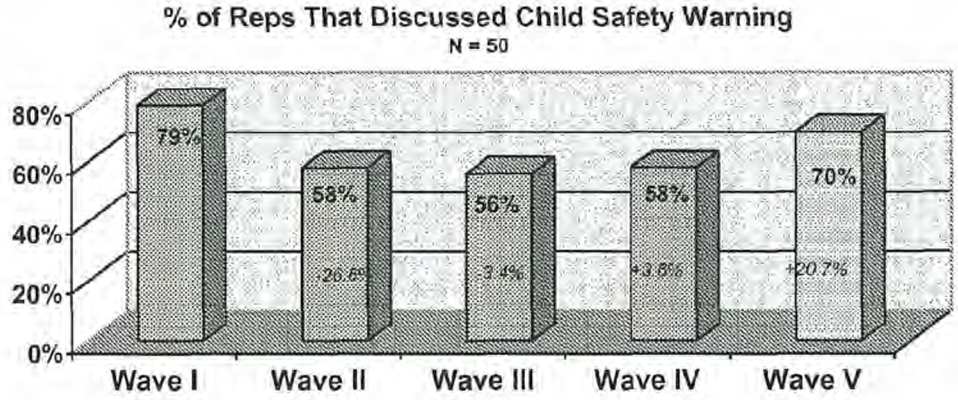
All participating physicians indicated that their respective Cephalon sales representatives discussed ACTIQ's indications with them. This is consistent with the prior four waves of research completed, as at least 92% of physicians in each wave reported that ACTIQ details included a discussion of indications for the product. The results of each wave are portrayed in the table below.



Appropriate patient selection for ACTIQ was reported to have been discussed by 46 of the 50 respondents (92%), with the remaining four respondents indicating that this topic had not been discussed with their Cephalon reps. This is an improvement from Wave IV (as seen in the chart below), and represents an increase of 10% relative to the findings from one year ago. This suggests that Cephalon reps are becoming increasingly more responsible and effective at communicating the patient types appropriate for ACTIQ therapy.

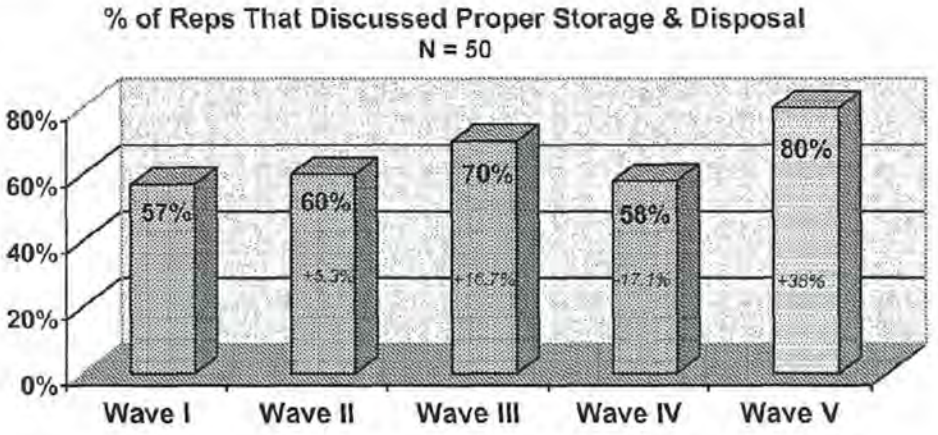


Seventy percent (70%) of respondents (35 of 50) reported that their Cephalon sales representatives had discussed the child safety warning. Seven physicians (14%) were unable to recall this topic and eight (16%) stated that the child safety warning had not been a topic of conversation during the detail. These percentages are significantly better than those reported in the past three waves, reinforcing the improvements that the sales force has made.



Forty (40) of the fifty participating physicians reported that proper storage and disposal of ACTIQ was discussed, an increase of 22 percentage points (and a relative increase of 38% of physicians) from Wave IV. Furthermore, this represents the greatest percentage of respondents that indicated storage and disposal of ACTIQ was discussed in any wave of research completed, dating back to August 2001. Clearly this is a notable achievement for the Cephalon sales force. Two respondents could not recall whether storage and disposal had

been discussed, and the eight remaining respondents stated that this topic had not been addressed.



When asked if they recalled any other safety issues that were covered as part of the ACTIQ detail, 12 physicians (24%) indicated that their reps had discussed one or more additional topics. These included the following:

Issue	# of Mentions
Side effects	3
Dosage titration	2
Hard to open without scissors	2
Prevention of abuse is important	2
Reminder for patients to brush teeth after using	2
Instruct patients not to chew it up and swallow it	1
Frequency of administration	1

Overall, the results from this wave of research are extremely positive for Cephalon. The sales representatives responsible for promoting ACTIQ have demonstrated much more diligence in conveying the necessary safety messages associated with the product.